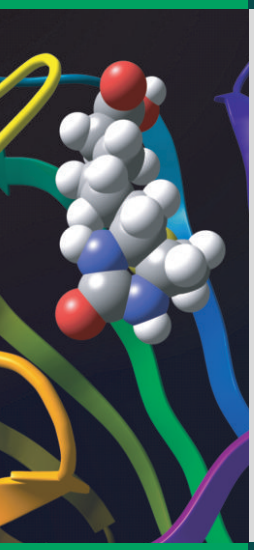


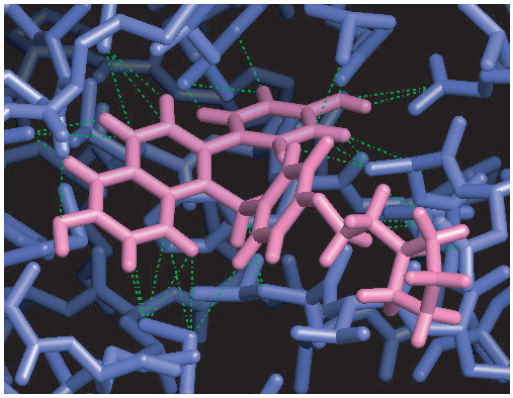
Glide

A complete solution for ligand-receptor docking

Glide offers the full spectrum of speed and accuracy from high-throughput virtual screening of millions of compounds to extremely accurate binding mode predictions, providing consistently high enrichment at every level.

SCHRÖDINGER.

The Advantages of Computational Docking



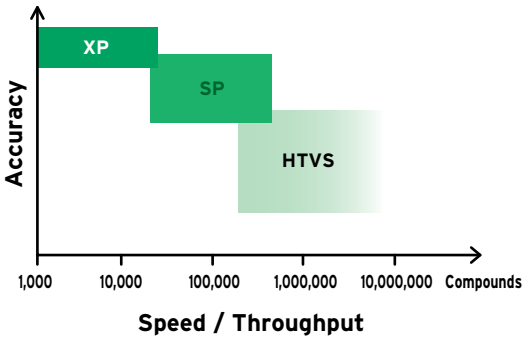
The LY-326315 ligand is shown docked in the active site of the human estrogen receptor. Maestro indicates favorable ligand-receptor interactions via dashed lines.

The widespread use of combinatorial chemistry and high-throughput screening (HTS) in the pharmaceutical and biotechnology industries means that large numbers of compounds can now routinely be investigated for biological activity. However, screening large chemical libraries remains an expensive and time-consuming process, with significant rates of both false positives and false negatives.

High-speed computational methods can now enrich the fraction of suitable lead candidates in a chemical database, thereby creating the potential to greatly enhance productivity and dramatically reduce drug development costs. With an ever-increasing number of drug discovery projects having access to high-resolution crystal structures of their targets, high-performance ligand-receptor docking is the clear computational strategy of choice to augment and accelerate structure-based drug design.

Glide: Maximizing Returns in Lead Discovery

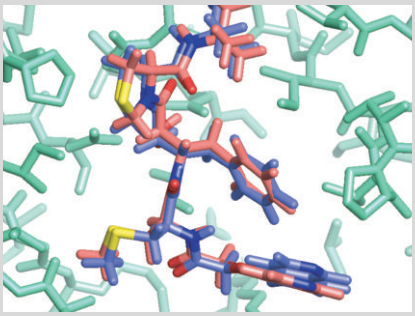
Glide offers the full solution for virtual screening from HTVS to SP to XP. The size of the dataset that needs to be studied at each level of accuracy is approximately an order of magnitude smaller than that of the previous, faster step. XP provides the most accurately docked poses and the highest level of enrichment.



Schrödinger's Glide is a ligand-receptor docking program specifically designed to bring speed, efficiency, and accuracy to lead discovery efforts. It provides the following benefits:

- **Complete solution:** Glide offers the full range of speed vs accuracy options, from the HTVS (high-throughput virtual screening) mode for efficiently enriching million-compound libraries, to the SP (standard precision) mode for reliably docking tens to hundreds of thousands of ligands with high accuracy, to the XP (extra precision) mode where further elimination of false positives is accomplished by more extensive sampling and advanced scoring, resulting in even higher enrichment.
- **Virtual screening:** Glide provides a rational workflow for virtual screening from HTVS to SP to XP, enriching the data at every level such that only an order of magnitude fewer compounds need to be studied at the next higher accuracy level.
- **Accurate binding mode prediction:** Glide reliably finds the correct binding modes for a large set of test cases. It outperforms other docking programs in achieving lower RMS deviations from native co-crystallized structures.
- **Universal applicability:** Glide exhibits excellent docking accuracy and high enrichment across a diverse range of receptor types.
- **Easy-to-use interface:** Glide easily automates calculations for large libraries of compounds and organizes docking results in both summary and detailed reports. Schrödinger's Maestro user interface also provides advanced visualization and analysis tools to examine ligand-receptor interactions.
- **Cross-platform support:** Glide supports Linux, SGI, and IBM/AIX. Entire databases can be run across multiple processors for maximum performance.

Performance-Driven Technology



The pepstatin analogue is shown docked inside the aspartyl proteinase penicillopepsin. Glide's best docking mode, shown in red, is in excellent agreement with the native ligand from the co-crystallized complex, shown in blue. The RMSD for this system is 1.10 Å.

Glide's unique blend of technology improves performance at every step of the process:

- **Identifying binding modes:** Glide exhaustively searches the protein active site for the best possible location and orientation for the docked ligand. Its unique flexible docking algorithm examines the conformational space, employing a heuristic screening process designed to eliminate unfavorable conformations. A series of hierarchical filters provide very high accuracy in predicting the ligand's binding mode, while reducing processing time by screening out unfavorable poses early in the process.
- **Rank-ordering ligands:** Schrödinger's GlideScore rewards favorable lipophilic, hydrogen bonding, and metal ligation contacts and penalizes frozen rotatable bonds and steric clashes. In addition, GlideScore incorporates a term proportional to the Coulomb-vdW interactions, as well as a small number of potential energy terms that reward hydrogen bond donors found in the active site's hydrophilic regions and penalize hydrogen bond donors and acceptors found in the hydrophobic regions. Glide's extra-precision (XP) mode combines a powerful sampling protocol with a custom scoring function that is specifically designed to eliminate false positives, thus further improving enrichment.
- **Setting up calculations and visualizing docking results:** The Maestro GUI provides an easy and efficient way to set up calculations and visualize docking results. Maestro's project facility makes it convenient to manage entire libraries from virtual screening to selecting leads for further analyses.

Enrichment Factors

The table below shows Glide enrichment factors, computed based on the rankings of active compounds seeded into a large library of presumed inactive molecules. EF (70%) lists database enrichment to recover 70% of all known actives, and EF (2%) lists database enrichment by examining only the top-ranked 2% of the database.

	Enrichment Factor	
Database Screen	EF (70%)	EF (2%)
Aldol Reductase	9	13
CDK-2 Kinase	8	10
Cox-2	11	24
DNA gyrase B	5	6
Estrogen Receptor	25	30
Gelatinase A	22	23
HIV Protease	34	27
HIV Reverse Transcriptase	5	8
Neuraminidase	20	21
p38 MAP Kinase	3	12
Squalene Synthase	33	30
Stromelysin	34	33
Thermolysin	54	35
Thrombin	31	31
Thymidine Kinase	15	21
Thymidylate Synthase	12	25

The crucial metric for assessing the performance of high-throughput docking codes is the extent to which a database of compounds could be enriched such that only a much smaller subset needs to be prepared and assayed to identify leads. Glide's effectiveness as a virtual screening tool is demonstrated by the consistently high enrichment factors it achieves across a diverse range of receptors representing a wide variety of active site moieties. Glide's broad applicability gives it an advantage over other docking programs, which may only perform well for one receptor class or binding motif.

Glide's success in pharmaceutical applications has been extensively and independently validated in a number of recent publications. A few examples include:

"Tryptophan 500 and Arginine 707 Define Product and Substrate Active Site Binding in Soybean Lipoxygenase-1", *Biochemistry*, **2004**, *43*, 13063-13071.

"A Detailed Comparison of Current Docking and Scoring Methods on Systems of Pharmaceutical Relevance", *Proteins*, **2004**, *56*, 235-249.

"Comparative evaluation of eight docking tools for docking and virtual screening accuracy", *Proteins*. **2004**, *57*, 225-242.

"Validation of Molecular Docking Calculations Involving FGF-1 and FGF-2", *J. Med. Chem.* **2004**, *47*, 1683-1693.

"Development and Characterization of Nonpeptidic Small Molecule Inhibitors of the XIAP/Caspase-3 Interaction", *Chemistry & Biology* **2003**, *10*, 759-767.

"Synthesis and Discovery of Macrocyclic Polyoxygenated Bis-7-azaindolylmaleimides as a Novel Series of Potent and Highly Selective Glycogen Synthase Kinase-3 Inhibitors", *J. Med. Chem.* **2003**, *46*, 4021-4031.

"Synthesis and SAR of Thrombin Inhibitors Incorporating a Novel 4-Amino-Morpholinone Scaffold: Analysis of X-ray Crystal Structure of Enzyme Inhibitor Complex", *J. Med. Chem.* **2003**, *46*, 3985-4001.

"Design, Synthesis, and Pharmacology of a Highly Subtype-Selective GluR1/2 Agonist, (RS)-2-Amino-3-(4-chloro-3-hydroxy-5-isoxazolyl)propionic Acid (Cl-HIBO)", *J. Med. Chem.* **2003**, *46*, 2246-2249.

"(S)-2-Amino-3-(3-hydroxy-7,8-dihydro-6H-cyclohepta[d]isoxazol-4-yl)propionic Acid, a Potent and Selective Agonist at the GluR5 Subtype of Ionotropic Glutamate Receptors. Synthesis, Modeling, and Molecular Pharmacology", *J. Med. Chem.* **2003**, *46*, 1350-1358.

"Synthesis of Novel Thrombin Inhibitors. Use of Ring-Closing Metathesis Reactions for Synthesis of P2 Cyclopentene- and Cyclohexenedicarboxylic Acid Derivatives", *J. Med. Chem.* **2003**, *46*, 1165-1179.

"Rational Design, Synthesis, and Pharmacological Evaluation of 2-Azanorbornane-3-exo,5-endo-dicarboxylic Acid: A Novel Conformationally Restricted Glutamic Acid Analogue", *J. Org. Chem.* **2003**, *68*, 1489-1495.

Evaluation Copies

To request an evaluation copy of Glide, please contact info@schrodinger.com. Our staff of support scientists will be happy to assist you in giving Glide a thorough trial.

Glide

A complete solution for ligand-receptor docking

System Requirements:

LINUX
- Pentium or better
- Linux kernel 2.4 (Red Hat 7.3) or later
- 256 MB memory

SGI
- R5000 or better
- IRIX 6.5.2m or later
- 256 MB memory

IBM AIX
- Power series
- AIX 4.3.3 or AIX 5.x
- 256 MB memory

Additional Information:

www.schrodinger.com
info@schrodinger.com

A Coordinated Family of Products

Schrödinger offers a coordinated family of drug discovery solutions. In addition to Glide, Schrödinger's structure based analyses contains two more integrated modules:

- **Liaison:** Ligand-receptor binding free energies for lead optimization
- **QSite:** Mixed QM/MM for reactive chemistry at the enzyme active site

Glide can be employed during lead discovery to dock candidate compounds, followed by Liaison or QSite to obtain more accurate structures and/or binding affinities during lead optimization.

Additionally, **MacroModel** can be instrumental in preparing both ligand and protein structures, and **QikProp** can predict accurate ADME properties for all lead compounds.

All Schrödinger products are seamlessly integrated through the Maestro graphical interface.

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